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ORIGINAL PAPER

Ten-year trends in benzodiazepine use in the Dutch population

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Abstract
Background In the past decades knowledge on adequate treatment of affective disorders and awareness of the negative consequences of long-term benzodiazepine use increased. Therefore, a decrease in benzodiazepine use is expected, particularly in prolonged use. The aim of this study was to assess time trends in benzodiazepine use.
Methods and material Data from the Longitudinal Aging Study Amsterdam (LASA) were used to investigate trends in benzodiazepine use between 1992 and 2002 in two population-based samples aged 55–64 years. Differences between the two samples with respect to benzodiazepine use and to sociodemographic, physical health and mental health characteristics were described and tested with chi-square tests and logistic regression analyses.
Results Benzodiazepine use remained stable over 10 years, with 7.8% in LASA-1 ($n = 874$) and 7.9% in LASA-2 ($n = 919$) ($p = 0.90$) with a persisting preponderance in women and in people with low education, low income, chronic physical diseases, functional limitations, cognitive impairment, depression, anxiety complaints, sleep problems and when using antidepressants. Long-term use remained high with 70% in 1992 and 80% in 2002 of total benzodiazepine use.
Conclusion In the Dutch population aged 55–64, overall benzodiazepine use remained stable from 1992 to 2002, with a high proportion of long-term users, despite the effort to reduce benzodiazepine use and the renewal of the guidelines. More effort should be made to decrease prolonged benzodiazepine use in this middle-aged group, because of the increasing risks with ageing.

Keywords Benzodiazepine use · Time trends · Population · Ageing

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Introduction

Benzodiazepines are widely used in the treatment of anxiety complaints, nervousness and sleep problems [4, 16, 30, 33, 34]. Although people may benefit from their anxiolytic and hypnotic effects, when used for a longer period (more than 2 months) benzodiazepine use may lead to addiction problems, with withdrawal symptoms, diminishing effect and difficulty in discontinuing treatment [43]. Particularly in later life, benzodiazepines have serious adverse effects, such as an increased risk of mobility and ADL problems [25, 26], falling [15, 29, 45, 51] and a negative effect on cognitive functioning [5, 10, 27, 28, 46, 54]. They can cause sedation and impairment of driving skills [39]. Mental and physical health and cognitive performance improve after discontinuation of benzodiazepines, particularly sleeping pills [1]. Despite these known side-effects, benzodiazepines are widely used, also by middle-aged and older people and often for long periods of time [2, 4, 16, 22, 30, 33, 34, 37, 38]. Although dose escalation is rare in older people [14, 52], discontinuation of benzodiazepine use is found to be more difficult with ageing, particularly after 45 years [12, 13, 20].

In the past decades depression and anxiety disorders have gained a lot of attention, leading to increasing emphasis on the importance of adequate treatment of these

disorders. The newer generation of antidepressants, the selective serotonine reuptake inhibitors (SSRI's), which are used in the treatment of depression as well as anxiety disorders, have become very popular and their use has shown a huge increase in the past decades [11, 40]. Also, the increasing knowledge of the impact of side effects and addiction problems of benzodiazepines has lead to the recommendation of short-term prescription and discontinuing use when possible, particularly in older people, with a preference for the short working benzodiazepines without pharmacologically active metabolites [28].

In the Dutch guidelines on pharmacological treatment of anxiety disorders serotonergic antidepressants are advised for pharmacological treatment. Benzodiazepines are recommended for short-term treatment only, in anxiety disorders as well as in mood disorders, with an exception of anxiety disorders that do no respond to two different SSRIs [3, 41]. Furthermore, in these years several types of psychotherapy have proven to be effective as well in anxiety and sleep disorders, e.g. exposure with response prevention and cognitive behaviour therapy, and they can be applied with or without pharmacotherapy [3, 49]. Thus, it might be expected that benzodiazepine use, and particularly long-term use, has decreased in the past years due to improved clinical practice. Another development that may have led to a decrease in benzodiazepine use is the increase of interest in and knowledge on physical and mental health issues in the general population in the past decades through the mass media and the more open communication. This has led to an increasing awareness of positive and negative consequences of drug use and an enhanced participation of patients in the process of medical decision-making.

In the literature, prevalence rates of benzodiazepine use vary between 2 and 17%, due to the variety in definitions of benzodiazepine use and observation period [60]. Conclusions on whether benzodiazepine use is stable in time are therefore not easily made. Consistent findings are that benzodiazepine use in women stays twice as high as in men, and that benzodiazepine use is higher in older people with a preponderance of long-term use [60].

Objectives

Our hypothesis is that in the past decades the development of special treatment for anxiety disorders, the introduction of SSRI's and the awareness of the addiction problems and the side effects of benzodiazepines have led to a decrease of benzodiazepine use, with a more adequate application and shorter use of benzodiazepines. We will investigate this in two population-based samples taking age, sex, income, education, physical problems, cognition, depression, anxiety, sleep problems, antidepressant use and alcohol use, into consideration. We chose this middle-aged group (55–64 years) because of the increasing risks of long-term benzodiazepine use when people grow older.

Methods

Sampling and procedures

Data were derived from the Longitudinal Aging Study Amsterdam (LASA), a longitudinal, interdisciplinary study on the predictors and consequences of changes in autonomy and well-being in the ageing population [18]. Baseline sampling procedures and characteristics of the sample have been described in detail in previous publications [6, 8, 17]. In short, the LASA sample is based on a representative random sample of 3,107 older adults between the ages of 55 and 85. The sample was drawn from the population registers of 11 municipalities in three regions of the Netherlands; each region consisted of one middle- to large-size city and two or more rural municipalities which bordered on the city, with numbers of inhabitants varying from 700,000 to 7,000 persons ($n = 3{,}805$, response rate 81.7%). The initial sample was stratified for age and sex and was weighted according to expected mortality at mid-term within each sex and age group, so that after 5 years equal numbers of men and women were expected to be alive in the separate age groups and that sufficient participants should be left to be examined after a period of 10 years. Non-response in the first LASA-cycle was related to age, but not to sex. Data-collection in LASA started in 1992–1993 (LASA-baseline) and participants were questioned every 3 years ever since. In 2002/2003 a new population sample was drawn, called LASA-2, by using the same sampling frame and procedures as for LASA-1. LASA-2 consisted of 1,002 respondents, with ages ranging from 55 to 64.

To address our research question, shifts in benzodiazepine use in 10 years, respondents of equal ages (55–64 years) from both samples were selected, resulting in 966 (LASA-1) and 1,002 (LASA-2) participants. Due to missing information on benzodiazepine use, samples of $n = 874$ (LASA-1) and 919 (LASA-2) were available for the analyses. In both samples this selection was not related to age, sex, or the other covariates.

All interviews were conducted in the homes of the respondents, by specially trained and intensively supervised interviewers. Informed consent was obtained from each respondent, according to the prevailing legal requirements. The study was approved by the Medical Ethical Committee of the VU University Medical Centre.

Measures

Use of benzodiazepines

Use of prescribed drugs was assessed in LASA-1 and LASA-2 by recording the medication from the drug containers in the home of the respondents, and the duration of use was registered. The anatomical-therapeutical-chemical (ATC) coding and categorization system for drug data coding [44] was used to classify all medication. Benzodiazepines were categorised as tranquillising agents (anxiolytics) or sleeping pills (hypnotics). Separate nominal variables were defined, indicating the use of anxiolytic drugs or hypnotic drugs (coded as 'yes' or 'no').

Duration of use was divided into four categories: short-term (<1 month), moderate (1 month–1 year), long-term (>1 year) and irregular (sometimes) use. When a respondent used more than one benzodiazepine, the longest use was counted.

The elimination time and the presence of pharmacologically active metabolites of the benzodiazepines were evaluated. The elimination time was considered long when half-life was >20 h. Presence (yes) or absence (no) of metabolites was established.

Covariates

Sex was investigated as a covariate, because of the preponderance of women in benzodiazepine use [23, 31, 42, 55, 57, 58], and in the prevalences of depression and anxiety disorders [32, 59].

Because *socio-economic status* is known to be associated with health status and health behaviour, and with benzodiazepine use [31, 55, 58], the level of education and the level of income were included as covariates.

The *level of education* was classified into three levels: low education (elementary school not completed, elementary education), medium education (lower vocational, general intermediate, intermediate vocational, general secondary education) and high education (higher vocational, college and university education).

Income was classified into three levels: low income (<1,000 Euros per month), intermediate income (1,000–3,000 Euros per month) and high income (more than 3,000 Euros per month). Income in LASA-1 was corrected for inflation of 3% per year until 2002.

Impaired *physical health* is associated with depression and anxiety complaints. Therefore, chronic diseases and functional limitations were included as independent variables.

Chronic diseases were assessed using specific questions on chronic non-specific lung disease, cardiac disease, peripheral atherosclerosis, stroke, diabetes mellitus, arthritis, malignant neoplasms and a maximum of two other chronic diseases. The total number of diseases ranged from 0 to 9. These data were cross-checked with the General Practitioners of the participants. Accuracy of self-report was shown to be independent of cognitive impairment, level of depressive symptoms and anxiety symptoms [36].

Functional limitations were measured with a questionnaire on difficulty experienced with several activities (walking up and down stairs, using public transportation and cutting own toenails). This questionnaire was validated in the Netherlands by Van Sonsbeek [50] and Kriegsman et al. [35].

Cognitive impairment might hamper recognition and treatment of affective disorders, but it can also be a side effect of benzodiazepine use. Cognitive impairment was measured with the Mini-Mental State Examination (MMSE), a frequently used screening instrument for global cognitive functioning. Scores range from 0 to 30 with higher scores indicating better cognitive performance. We used the cut-off score of 23, with scores ≤23 indicating cognitive impairment [21].

Excessive *alcohol consumption* may be an indication for addiction problems, but it can also be used as self-medication in the case of withdrawal symptoms in excessive benzodiazepine use. Alcohol consumption was assessed with a questionnaire developed for the Netherlands Health Interview Survey [53] and classified according to the Garretsen Index of Present Alcohol Use [24], into three categories (excessive/severe, moderate/light and non-drinker).

Depressive symptoms, anxiety symptoms and sleep problems, often the reason for benzodiazepine use, were measured with the Centre for Epidemiologic Studies Depression Scale (CES-D), a 20-item self-report scale developed for use in the community [7, 47, 48]. The CES-D ranges from 0 to 60 with higher scores indicating more depressive symptoms. The dichotomous score based on the commonly used cut-off score of 16 was used [9] to indicate clinically relevant depressive symptoms. Although the CES-D was designed for the screening of depressive symptoms, it may also be used as a screener of anxiety symptoms [7]. We used the particular CES-D item about feelings of nervousness and tension (item number 10: feeling fearful) to measure *anxiety*. To investigate *sleep problems* we used CES-D item number 11 (sleep being restless). This item had a good correlation with a larger questionnaire in LASA on sleep problems and could therefore be used as an indicator of sleep problems.

Antidepressant use was measured in the same way as benzodiazepine use, i.e. based on information on the drug containers, provided by the respondents. A separate nominal variable was defined, indicating the use of antidepressant drugs, coded as 'yes' or 'no'.

Statistical analyses

In order to investigate time trends, i.e. changes over time in benzodiazepine use, the data had to be made suitable for comparing the two cycles. Therefore, prevalence data were weighted by age and sex, in order to reach a similar distribution of age and sex in the two study samples, with LASA-1 as the reference. To investigate the differences in benzodiazepine use between LASA-1 and LASA-2, i.e. to make a comparison between the two samples possible, we pooled the data from both samples and added the factor 'time' by defining the variable 'sample number' (1 = LASA-1 and 2 = LASA-2). In this pooled data file, first, for descriptive purposes, the differences between LASA-1 and LASA-2 with respect to benzodiazepine use and all covariates were tested using chi-square tests. Likewise, the differences between LASA-1 and LASA-2 within the groups of benzodiazepine users with respect to the covariates were tested using chi-square tests. In the pooled sample, associations of benzodiazepine use with the separate covariates were investigated in bivariate analyses using chi-square tests. To investigate the association of time and the other covariates with benzodiazepine use in a multivariate model, logistic regression analyses were performed, with benzodiazepine use as the dependent variable, and with time and the other covariates entered stepwise into the model. To investigate effect modification of the covariates on time differences in benzodiazepine use, logistic regression analyses with interaction-terms of time with the covariates were performed. In the chi-square tests and the logistic regression analyses, p values lower than 0.05 were regarded as statistically significant.

Results

An overview of the characteristics and the differences between LASA-1 and LASA-2 is shown in Table 1. Benzodiazepine use showed no major difference between the two samples with 7.8% in LASA-1 and 7.9% in LASA-2 ($p = 0.90$), nor did separate rates of tranquillising agents (3.7 and 4.8% resp., $p = 0.24$) and sleeping pills (4.6 and 3.9% resp, $p = 0.49$). In both samples the majority of the benzodiazepines was used for a long period. In LASA-1 26% was used during a month to a year, and 69% was used longer than 1 year. In LASA-2 these percentages were 15 and 80%. Use of short-working benzodiazepines without pharmacologically active metabolites increased from 56% in LASA-1 to 65% in LASA-2.

As a consequence of the weighing procedure, age and sex were equally distributed in the two samples. In LASA-1 47.9% were men and in LASA-2 47.2% were men,

Table 1 Socio-demographic characteristics, physical and mental health and benzodiazepine use in LASA-1 and LASA-2

	LASA-1		LASA-2		Sample differences p value
	$N = 874$		$N = 919$		
	N	%	N	%	
Education					
Low	268	30.7	188	20.5	0.00
Intermediate	479	54.8	532	57.9	
High	127	14.5	199	21.7	
Income[a]					
Low	135	18.9	100	11.9	0.00
Medium	370	51.7	365	43.5	
High	211	29.5	375	44.6	
Chronic diseases					
None	310	35.5	243	26.4	0.00
One or more	564	64.5	676	73.6	
Functional limitations (of #3)					
None	725	83.0	667	72.6	0.00
One or more	149	17.0	252	27.4	
Cognitive impairment					
No: MMSE >23	848	97.0	888	96.6	0.52
Yes: MMSE ≤23	26	3.0	31	3.4	
Depression					
No	781	89.4	790	86.0	0.03
Yes (CESD ≥16)	93	10.6	129	14.0	
Anxiety: being fearful					
No	785	89.8	803	87.4	0.16
Sometimes—often	89	10.2	116	12.6	
Sleep problems					
Never/some of the time	753	86.2	758	82.5	0.03
Occasionally often—always	121	13.8	161	17.5	
Use of alcohol					
Never	129	14.8	75	8.2	0.00
Light—moderate	683	78.1	744	80.9	
(very) excessive	62	7.1	100	10.9	
Antidepressant users					
No	861	98.5	883	96.1	0.00
Yes	13	1.5	36	3.9	
Benzodiazepine users					
All	68	7.8	73	7.9	0.90
Anxiolytic users	32	3.7	44	4.8	0.24
Hypnotic users	40	4.6	36	3.9	0.49
Length of benzodiazepine use[b]					
Short term (<1 month)	3	5.5	4	5.5	0.34
Moderate (1 month–1 year)	14	25.5	11	15.1	
Long term (>1 year)	38	69.1	58	79.5	
Long half-life and/or active metabolites of benzodiazepines					
No	38	55.9	47	64.4	0.30
Yes	30	44.1	26	35.6	

[a] In the questionnaire about income, respondents were able to choose the option 'wishes not to answer'; this resulted in 'no answer' in 158 respondents (18.1%) in LASA-1 and in 79 respondents (8.6%) in LASA-2. This category was left out of the analyses

[b] In LASA-1 duration of benzodiazepine use was not known in 13 respondents (19.1%), leaving 55 out of 68 benzodiazepine users available for the analyses in length of benzodiazepine use

$p = 0.76$. Mean age in LASA-1 was 59.7 years, and in LASA-2 this was 59.4 years.

The second sample was higher educated and had a higher income despite the inflation correction. Furthermore, respondents in LASA-2 reported more chronic diseases and functional limitations, and showed more depressive symptoms. They also reported more sleep problems. The presence of cognitive impairment and anxiety symptoms remained rather stable in the two samples. In LASA-2 more respondents used alcohol and there was also a rise in the amount of alcohol used. Furthermore, there was a remarkable increase of antidepressant use.

Table 2 shows time differences in benzodiazepine use in the socio-demographic and health subgroups and associations of benzodiazepine use with these subgroups in the pooled sample. Although an increase of benzodiazepine use was found in several subgroups (e.g. in women, in respondents with low education or low income, and in the case of depression, anxiety and sleep problems) and a decrease in other subgroups (e.g. men, high education, high income, and antidepressant users), these differences were not statistically significant, probably due to the small numbers in several subgroups.

In the pooled sample, benzodiazepine use was significantly higher in women, and in the respondents with chronic physical disease, functional limitations, cognitive impairment, depression, anxiety, sleep problems and when using an antidepressant. Benzodiazepine use was lower in respondents with higher education, higher income and with higher alcohol use.

Table 3 shows the odds ratios for benzodiazepine use and time and the other covariates. The bivariate logistic regression analyses showed statistically significant associations of benzodiazepine use all covariates, but not with time and age. In the multivariate regression analyses, controlling for all covariates including time, benzodiazepine use was found to be associated with female sex, and with the presence of one or more chronic diseases, depression, sleep problems and antidepressant use.

Investigation of the interaction between time and the independent variables did not show any statistically significant interaction (results not shown).

Discussion

In the present study shifts in benzodiazepine use from 1992 to 2002 were investigated in a population-based sample aged 55–64 years.

We expected a decrease of benzodiazepine use due to enhanced knowledge of the effects of long-term benzodiazepine use and insight into adequate treatment of depression, anxiety and sleep problems. However, benzodiazepine use remained stable. Furthermore, long-term use remained high despite recommendations in the guidelines to keep treatment short. However, compared with the increase of antidepressant use in this period, the stability in benzodiazepine use may be considered a relatively positive finding. A trend in preference was found for short-working benzodiazepines without pharmacological active metabolites, which is also a positive finding in this middle-aged group.

In our study, several socio-demographic characteristics and physical health and mental health factors that are known to be associated with benzodiazepine use showed differences in the two samples. We found a decrease in the prevalence of low income and low education, and an increase in the prevalence of physical health problems, depression, sleep problems, alcohol use and antidepressant use. However, the shifts in the presence of these characteristics and risk factors did not affect their associations with benzodiazepine use, nor did age or sex: all factors except time and age were associated with benzodiazepine use. This is in line with the literature [38]. Being a woman, having one or more chronic diseases, depression, sleep problems and the use of antidepressant remained associated with benzodiazepine use in the multivariate analyses and were considered to explain the association with the other risk factors.

In 2002, women and respondents with low education still used more benzodiazepines. Respondents with chronic physical disease and functional limitations still used more benzodiazepines. Although they may diminish feelings of distress and sleep problems, they can also cause sedation, muscle weakness and increase the risk of falling in this physically vulnerable group. In the respondents with cognitive impairment, benzodiazepines are often used successfully to reduce concomitant anxiety and sleep disturbances, but they may increase memory problems and reduce attention, alertness and mental speed. In the case of depression, anxiety and sleep problems, benzodiazepine use remained high, although it is recommended only for short-term use or for support in the first weeks of treatment with antidepressants or psychotherapy. Prolonged use of benzodiazepines may even worsen the depressive symptoms [19, 56].

The combination of benzodiazepine use and the use of alcohol is important because of the possibility of excessive sedation and mood disturbances. In the alcohol users benzodiazepine use was lower than in the full sample, but some respondents combined alcohol with benzodiazepine, which may lead to important health problems, e.g. a higher risk of falling, memory problems and traffic accidents, particularly when this group gets older.

Table 2 Benzodiazepine use by socio-demographic and health measures in LASA-1 and LASA-2 and in the pooled sample (LASA 1 + 2)

Subgroups	LASA-1 $N = 874$		LASA-2 $N = 919$		Time differences for the subgroups p value	LASA 1 + 2 pooled sample $N = 1{,}793$		Subgroup differences (in pooled sample) p value
	Benzodiazepine users		Benzodiazepine users			Benzodiazepine users		
	N	% in subgroup	N	% in subgroup		N	% in subgroup	
Sex								
Men	21	5.0	14	3.2	0.19	35	4.1	0.00
Women	47	10.3	59	12.2	0.37	106	11.3	
Education								
Low	25	9.3	22	11.7	0.41	47	10.3	0.02
Intermediate	34	7.1	44	8.3	0.49	78	7.7	
High	9	7.1	7	3.5	0.15	16	4.9	
Income								
Low	16	11.9	15	15.0	0.48	31	13.2	0.00
Medium	23	6.2	27	7.4	0.53	50	6.8	
High	15	7.1	22	5.9	0.55	37	6.1	
Chronic diseases								
None	12	3.9	8	3.3	0.72	20	3.6	0.00
One or more	56	9.9	65	9.6	0.85	121	9.8	
Functional limitations								
None	46	6.3	40	6.0	0.79	86	6.2	0.00
One or more	22	14.8	33	13.1	0.64	55	13.7	
Cognitive impairment								
No: MMSE >23	63	7.4	67	7.5	0.93	130	7.5	0.00
Yes: MMSE ≤23	5	19.2	6	19.4	0.99	11	19.3	
Depression								
No (CESD <16)	47	6.0	42	5.3	0.55	89	5.7	0.00
Yes (CESD ≥16)	21	22.6	31	24.0	0.80	52	23.4	
Anxiety: being fearful								
No	53	6.8	49	6.1	0.60	102	6.4	0.00
Sometimes—often	15	16.9	24	20.7	0.49	39	19.0	
Sleep problems								
Never—sometimes	47	6.2	36	4.7	0.20	83	5.5	0.00
Occasionally often—always	21	17.4	37	23.0	0.25	58	20.6	
Use of alcohol								
Never	15	11.6	12	16.0	0.37	27	13.2	0.00
Light—moderate	51	7.5	56	7.5	0.97	107	7.5	
(very) Excessive	2	3.2	5	5.0	0.59	7	4.3	
Antidepressant use								
No	62	7.2	63	7.1	0.96	125	7.2	0.00
Yes	6	46.2	10	27.8	0.23	16	32.7	

Strength and limitations of the study

There are some limitations to this study. Access to two large population-based samples with data concerning a wide variety of relevant variables makes LASA very well suited for an investigation of trends in benzodiazepine use. However, within specific subgroups, the numbers using benzodiazepines were small, which limits statistical analyses in subgroups. A second limitation of the present study is the use of self-reports. This may cause report bias, due to problems in the recall of information from the past (chronic disease), or to unwillingness or feelings of shame (income,

Table 3 Odds Ratios with 95% CI for benzodiazepine use and time, sociodemographic and health measures, unadjusted and adjusted for all co-variates, in the pooled sample

	Benzodiazepine use in the pooled sample			
	Unadjusted		Adjusted	
	OR	95% CI	OR	95% CI
Time	1.02	0.73–1.44	0.80	0.54–1.18
Female sex	**2.97**	**2.00–4.41**	**2.31**	**1.50–3.57**
Older age group	1.09	0.77–1.54	1.00	0.69–1.45
Higher education	**0.69**	**0.53–0.90**	0.95	0.70–1.30
Higher income	**0.79**	**0.68–0.94**	0.99	0.82–1.20
One or more chronic diseases	**2.88**	**1.78–4.68**	**1.86**	**1.11–3.10**
One or more functional limitations	**2.41**	**1.69–3.46**	1.26	0.82–1.93
Cognitive impairment	**2.95**	**1.50–5.84**	1.70	0.77–3.80
Depression	**5.09**	**3.49–7.43**	**2.28**	**1.43–3.64**
Anxiety	**3.42**	**2.29–5.12**	1.38	0.86–2.24
Sleep problems	**4.46**	**3.10–6.41**	**2.29**	**1.50–3.50**
Use of alcohol	**0.54**	**0.37–0.78**	0.83	0.55–1.26
Antidepressant use	**6.28**	**3.36–11.72**	**3.71**	**1.83–7.52**

education, alcohol use). However, the main variable in this study, medication use, was recorded directly from the containers and did not rely on self-report.

Conclusion

It was concluded that benzodiazepine use in this middle-aged population sample remained stable from 1992 to 2002, with a majority of long-term use, despite recommendations in the guidelines for short-term use. Benzodiazepine use remained higher in women, and in respondents with low education, low income, chronic physical disease, functional limitations, depression, anxiety complaints, sleep problems and in those using an antidepressant. More attention should be paid to reduce benzodiazepine use in the middle-aged, in order to diminish its increasing negative effects on health and functioning when getting older. In the case of long-term use, discontinuation programmes with a tapering-off procedure may be helpful.

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